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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Francisco <i>et al.</i>		
Serial No.: 09/724,406		Group Art Unit: 1642
Filed: November 28, 2000		Examiner: Yu, Misook
For:	RECOMBINANT ANTI-CD30 ANTIBODIES AND USES THEREOF	

**DECLARATION OF KERRY KLUSSMAN
UNDER 37 CFR § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Kerry Klussman, do declare and state that:

1. I am a citizen of the United States residing at: 2315 N. 82nd St. Seattle, WA 98103.
2. From 08/99 to the present, I have been employed by Seattle Genetics, Inc., assignee of the above identified application, initially as Research Associate from 08/99 to 04/00 and presently as Sr. Research Associate from 04/00 to 11/04. I received the degree of Bachelor of Science from Seattle Pacific University in Biology in 1991.
3. My academic and technical experience and honors, and a list of my publications are set forth in my curriculum vitae, attached hereto as Exhibit 1.

¹
EXHIBIT A

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4. I have reviewed the Public Protest Against U.S. Serial No. 09/724,406 Under 37 CFR § 1.291 (Second Submission) ("Public Protest") dated April 16, 2004, the accompanying Declaration by Dr. Robert F. Graziano Under 37 CFR 1.132 in Support of the Public Protest Against U.S. Serial No. 09/724,406 ("Declaration of Dr. Graziano") dated April 16, 2004, and the instant application and claims.
5. I am making this declaration to provide evidence that the subject matter of the claims in the above referenced patent application are not described by Pohl *et al.*, 1993, *Int. J. Cancer* 54:418-425 and Falini *et al.*, 1992, *Brit. J. Haematology* 82:38-45.
6. I have reviewed Pohl *et al.* Contrary to paragraph 4 of the Declaration of Dr. Graziano, Pohl *et al.* do not describe the *in vivo* use of HRS-4 to treat Hodgkin's Disease in animal models. On page 422, second column titled *Prevention of Tumor Growth in vivo by Ab3 4A4*, Pohl *et al.* tested the ability of Ab3 4A4 to prevent tumor growth *in vivo*. Pohl *et al.* describe the pretreatment of SCID mice with HRS-4. (Pohl *et al.*, page 422, right hand column, first full paragraph). One hour subsequent to pretreatment with HRS-4, the SCID mice were subcutaneously injected with a number of L540 tumor cells. Pohl *et al.* do not describe a study where SCID mice with established tumors were treated with HRS-4.
7. I am also making this declaration to provide evidence that one of skill in the art, following the conditions described in the application, without undue experimentation, could conduct assays to select the antibodies in the claims.
8. I conducted *in vitro* experiments in February 2000 using Ber-H2 in the same soluble and immobilized assays described in the application. In my studies, which I will further describe below, Ber-H2 did not exert a cytostatic or cytotoxic effect on a HD cell line. By conducting the soluble and immobilized studies described in the application with Ber-H2, AC10, and He-F1, I was able to select antibodies that possess the

property of being able to exert a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, wherein said antibody exerts the cytostatic or cytotoxic effect on the Hodgkin's Disease cell line in the absence of conjugation to a cytostatic or cytotoxic agent and in the absence of cells other than cells of said Hodgkin's Disease cell line.

9. Dr. Graziano states that he conducted studies using Ber-H2 and HRS-4 "in the same cytostatic cross-linking assays described in the application." (Declaration of Dr. Graziano, para. 4). From the Public Protest and the Declaration of Dr. Graziano, the conditions employed in the studies described by Dr. Graziano are as follows:

The cells were cultured in flat-bottomed, 96 well tissue culture plates in a final volume of 200 μ l/well (in triplicate). The anti-CD30 antibodies were added to the cell lines to a final concentration of 2 μ g/ml. Secondary cross-linking antibody was added to the final concentration of 8 μ g/ml. After 96 hours, the plates were pulsed with 3 H-thymidine (0.5 μ Ci/well), and incubated for an additional four hours before harvesting and counting on a scintillation counter. Page 3, Public Protest.

I cultured the cells in flat-bottomed, 96 well tissue culture plates in a final volume of 200 μ l/well (in triplicate) and added the anti-CD30 antibodies to the cell lines to a final concentration of 2 μ g/ml and the secondary cross-linking antibody to a final concentration of 8 μ g/ml. After 96 hours, I pulsed the plates with 3 H-thymidine (0.5 μ Ci/well) and incubated for an additional four hours before harvesting and counting on a scintillation counter. Para. 6, Declaration of Dr. Graziano.

10. However, the conditions used by Dr. Graziano in his studies are not the same as the conditions in the cross-linking experiment described in Example 6 of the current application on page 50, lines 25-30. The conditions differ by at least the:
- a. amount of secondary cross linking antibody (8 μ g/ml used by Dr. Graziano vs. 20 μ g/ml used in the Example),
 - b. concentration of cells used by Dr. Graziano is unknown (50,000 or 5,000 cells/well in the Example),

- c. incubation time (96 hours by Dr. Graziano vs. 72 hours in the Example), and
 - d. amount of ^3H -thymidine (0.5 $\mu\text{Ci}/\text{well}$ used by Dr. Graziano vs. 1 $\mu\text{Ci}/\text{well}$ for the final 5 hours in the Example).
11. Although Dr. Graziano appears to have used less secondary cross linked antibody in his study, he fails to provide the concentration of cells/well. Absent this information, one cannot determine the ratio of secondary cross linked antibody:cells/well.
 12. Further, in my opinion, the use of a secondary cross-linking antibody can induce activity of an antibody.
 13. Dr. Graziano was provided with conditions for conducting a secondary cross-linking assay in the application. Dr. Graziano chose to perform his experiment using different conditions than those described in the application.
 14. Under the direction of the inventors in the current application, I conducted *in vitro* studies using the conditions described in Example 6, pages 50-52, of the current application in February 2000. I tested an anti-CD30 antibody, referred to as Ber-H2, in the soluble and immobilized assays described in the current application.
 15. I used the following cell lines: L540 (Hodgkin's lymphoma derived cell line with a T cell phenotype) and L428 (Hodgkin's lymphoma derived cell line with a B cell phenotype). I cultured the L540 and L428 cells in flat-bottom, 96 well plates at a density of 50,000 or 5,000 cells/well in growth media RPMI with 10% fetal bovine serum (FBS) for cell line L428 and RPMI/20% FBS for cell line L540.
 16. To evaluate the biological activity, I cultured the CD30-expressing HD cell lines (either 50,000 cells/well or 5,000 cells/well) in the presence of soluble or immobilized Ber-H2, AC10 and He-Fi-1 antibodies and a third prior art anti-CD30 antibody (as a control) referred to as Ki-1 (previously shown to have no effect on HD cell lines, Gruss *et al.*, 1996, Blood 83:2045-2056).

(previously shown to have no effect on HD cell lines, Gruss *et al.*, 1996, Blood 83:2045-2056).

17. As shown in Figures 1a-b and 2a-b, Exhibits to my Declaration, neither immobilized nor soluble Ber-H2 had cytotoxic effects on the HD cell lines L428 and L540.
18. The data described in this declaration confirm that the prior art antibodies Ki-1 and Ber-H2 do not exert a cytostatic or cytotoxic effect on HD cell lines.
19. At least Example 6, on pages 50-52, of the current application provides the conditions for conducting assays for antibodies having the properties of immunospecifically binding CD30 and exerting a cytostatic or cytotoxic effect on a HD cell line, wherein the antibodies exert the cytostatic or cytotoxic effect on the HD cell line in the absence of conjugation to a cytostatic or cytotoxic agent and in the absence of cells other than cells of said HD cell line.
20. I have reviewed Falini *et al.* I agree with Dr. Graziano that Falini *et al.* do not conclude that Ber-H2 can be used to "treat Hodgkin's Disease *in vivo* (in patients)." (Declaration of Dr. Graziano, para. 4).
21. My experiments conducted in February 2000 with Ber-H2 described above showed a lack of *in vitro* activity of Ber-H2. My experiments also showed *in vitro* activity of AC10 and He-Fi-1.
22. The results of my experiment showing a lack of activity of Ber-H2 *in vitro* correlates with the *in vivo* data of Falini *et al.*
23. The data described in this declaration confirms that there is guidance in the application for the claims since the application provides guidance for selecting anti-CD30 antibodies having the claimed therapeutic property of treating HD and, thus, would not require undue experimentation to make and use the invention as claimed.
24. I declare further that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are

made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 11/5/04


Kerry Klussman

Attachments:

Exhibit 1: Curriculum Vitae of Kerry Klussman

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